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REVIEW ARTICLE

Shogaol: Current Evidence of its Positive Impact on Well-being

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Abstract

Natural products are widely recognised for their cost-effectiveness, safety and good tolerance in the prevention and remedy for numerous health issues. Ginger rhizome, a common spice, is extensively used as a natural remedy for addressing diverse health issues. It has a wide range of biologically active constituents, including both volatile and non-volatile ones. Research indicates that it significantly lessens amnesia brought on by ageing naturally. The ginger extract includes 6-shogaol, the main bioactive ingredient. The name "shogaol" comes from the Japanese term for ginger. A strong ginger component of Shogaols has a structural similarity to gingerol. Out of the group, 6-shogaol is the most prevalent. Shogaol, the primary active element found in dried ginger or through the dehydration of gingerol during long-term storage, has received recognition for its pharmacological effects, including antibacterial, antioxidant, anticancer, anti-inflammatory, anti-obesity, and antiemetic. It improves cognitive functions, safeguards against neurodegenerative disorders, helps to reduce pain and inflammation, promotes digestive health and potentially prevents cancer cell growth and proliferation. This review consolidates the current research findings on the therapeutic benefits of Shogaol.

Keywords: Biological Activity, Gingerol, Ginger Rhizome, Natural Remedy, Shogaol

1. Introduction

In Chinese, Western, and traditional Ayurvedic systems of medicine, ginger rhizome (*Zingiber officinale* Roscoe), a monocotyledonous herb which belongs to the family of Zingiberaceae, is widely used to treat illnesses, such as headaches, respiratory conditions, nervous system disorders, cardiovascular conditions, nausea, vomiting and abdominal discomfort[1-3]. Numerous pharmacological investigations and systematic reviews have consistently shown Ginger's positive impact on human health, such as improving metabolic syndrome, inflammation, digestion and treatment of cancer. Recently, ginger gained significant attention as a natural home treatment for COVID-19 and for easing the respiratory symptoms associated with SARS-CoV-2 infections[4,5].

Ginger rhizomes are rich in various phytochemical constituents. So far over 400 bioactive volatile and nonvolatile components have been found. These components have been classified into many active chemical groups, including monoterpenes (limonene, citral, α/β-pinenes and cineole), phenolics (gingerols, diaryl heptanoids (curcumin), 6-shogaol, sesquiterpenes (β-elemene, farnesene, 6-paradol and zingerone)[6-8]. Among these gingerols rich in fresh ginger and shogaols rich in dried ginger or gingerol is the precursor of shogaol. Several pharmacological studies and systematic reviews evidenced that gingerol possesses several pharmacological properties like antiemetic, anti-inflammatory, antitumor, antiobesity, hepatoprotective, antioxidant, cardioprotective, renoprotective effects, immunomodulatory effects and antimycobacterial activity against tuberculosis[9-12].

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Fresh ginger is dried, and the active constituent gingerol is converted to shogaol depending upon the drying temperature. Shogaol which is twice as pungent as gingerol and it shows more biological medicinal activity (anti-inflammatory, antioxidant, neuroprotective and anti-tumour action) has sparked widespread interest in recent years. It emerged as a viable natural alternative with a unique ability to affect the cellular pathways of specific diseases. This review seeks to give an in-depth exploration of shogaol's pharmacokinetic, bioavailability and mechanism of action for its therapeutic effects[13,14]. Accordingly, it intends to provide the key findings of shogaol's salutary effect on human health.

1.1 Shogaol

Shogaol ($C_{17}H_{24}O_3$; MW of 276.376 $g.mol^{-1}$) is the phenolic compound present in dried ginger, such as 6-,8 and 10- Shogaol, in the chemical structure displayed (Figure 1).

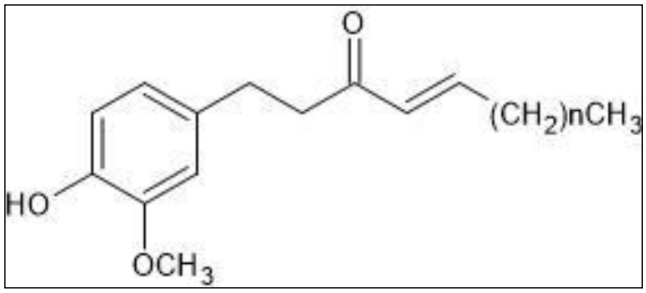
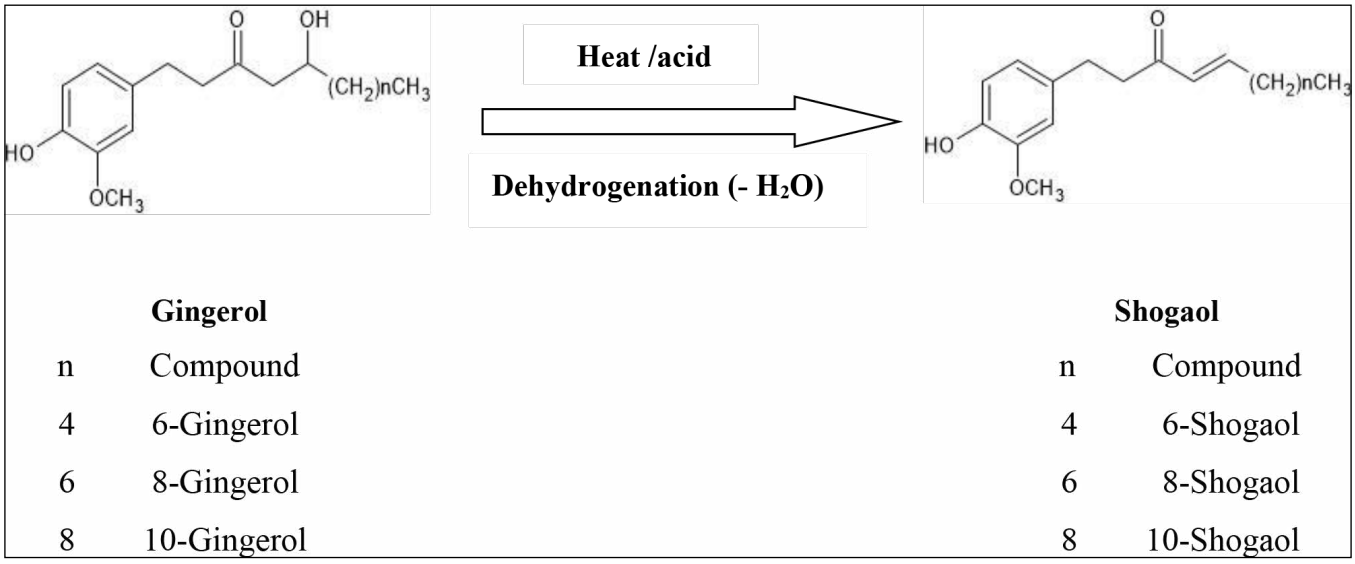


Figure 1. Structure of Shogaol.

Shogaol is prepared from gingerol by heat-facilitated dehydration/acid-catalysed method and long storage conditions, owing to the transformation of β-hydroxyl ketone to α, β- unsaturated ketone (Figure 2). 6-Shogaol obtained from the ginger pulp at 190°C/15 min, the yield value is 0.39 ± 0.03 mg/g, the yield value increased with the increasing temperature and time because of thermal cracking which converts gingerol to Shogaol[15,16].

Shogaol is obtained from ginger in different drying methods such as Hot Air Drying (HAD), Open Sun Drying (OSD) and Solar Tunnel Drying (STD) with various temperatures (120, 150 and 180°C) and time. From these methods, the content of 6-,8- and 10-Shogaol is higher in HAD method (120°C - 3.02 ± 0.78; 2.16 ± 0.26; 2.04 ± 0.18, 150°C - 3.93 ± 0.53; 2.62 ± 0.21; 3.05 ± 0.33,180°C - 2.58 ± 0.11; 1.73 ± 0.06; 1.41 ± 0.02) which was shown in High Performace Liquid Chromatography (HPLC) analysis method[14]. Using the LC-MS-MS approach, shogaol was identified from ginger extract. At m/z 275, 303, and 331 negative ion electrospray reveals deprotonated molecules of 6-, 8-, and 10-Shogaol. In contrast, the benzylic cleavage at the C1-C2 bond produced base peaks at m/z 139, 167 and 195. During tandem mass spectrometry and collision-induced dissociation, a neutral loss of 136u (2-methoxy-4-methylenecyclohexa-2, 5-dienone) was



Gingerol		Shogaol	
n	Compound	n	Compound
4	6-Gingerol	4	6-Shogaol
6	8-Gingerol	6	8-Shogaol
8	10-Gingerol	8	10-Shogaol

Figure 2. Synthesis of Shogaol from Gingerol.

observed. The structure of shogaol, at C5, is absent in the hydroxyl group and possesses a double bond at C4-C5, which mitigated atomisation at C4-C5[17].

The pharmacokinetic property of ginger root (1g) was evaluated in healthy human subjects via oral administration and 6- shogaol was quickly taken up and identified in serum as glucuronide conjugates. The Cmax, AUC and Tmax values were estimated for 2g dose of ginger root showed 6-Shogaol 0.15±0.12 µg/mL; 10.9±13.0 µg·hr/mL; 65.6±22.6 mins and elimination half-life< 2hr[18]. The metabolism of 6-Shogaol was examined using mice (oral route) and cancer cells. Using HPLC analysis as a basis using a mouse faecal sample, thirteen metabolites (M1–M13) were discovered and mass spectra were used to clarify the structures of seven of the metabolites[19]. Shogaol has a stronger affinity for fat and is quickly absorbed, reducing its bioavailability. Some studies suggest that combining shogaol with bio-enhancers can increase its bioavailability. The dosage varied depending on whether it was taken as powder or oil, but preclinical and clinical studies revealed that 1-2g/day was tolerated.

2. Biological Activity of Shogaol

Shogaol has a wide range of beneficial effects on human health. This study publishes the currently available records and updates of biological activity (Tables 1 and 2, Figure 3).

2.1 Antioxidant Activity

Active oxygen is created during regular metabolic processes and serves a variety of biological purposes. However, excessive synthesis of active oxygen can lead to antioxidant imbalance, a key factor for the progression of numerous diseases. Oxidative stress results in the overproduction of Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS), which causes an imbalance in the body's ability to neutralise free radicals through antioxidants. Redox imbalance assessment typically involves the use of diagnostic indicators, such as nuclear factor erythroid 2-related factor 2 (Nrf2), Malondialdehyde (MDA), Superoxide Dismutase (SOD) and Lactate Dehydrogenase (LDH).

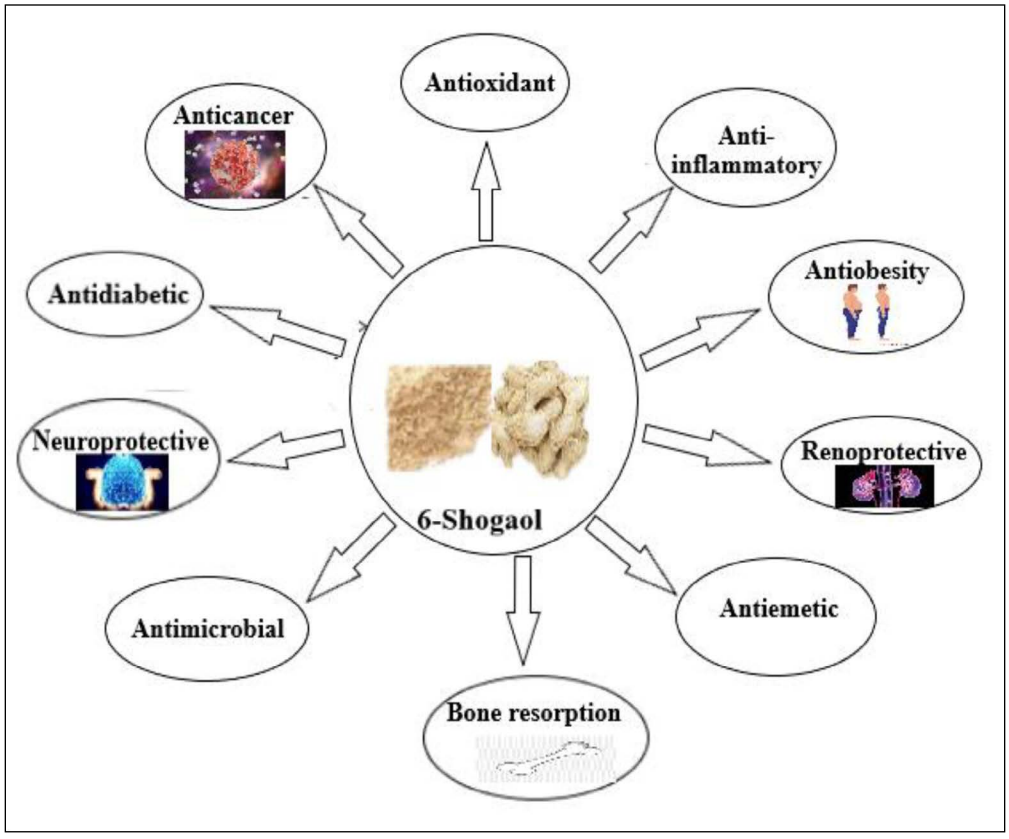


Figure 3. Biological activity of Shogaol.

6-Shogaol substantially reduces the overexpression of the Oxidation Resistance Protein (OXR)-1-P53 axis, which might promote ubiquitination or neddylation and thus lead to the degradation of p53 through increased Skp Cullin F Box (SCF) complex assembly by extension and shield Vascular Smooth Muscle Cells (VSMCs) from apoptosis[20]. The Nrf2 signalling pathway is a crucial defence against oxidative damage, which upregulates the free radical scavenger heme oxygenase 1's (HO-1) mRNA expression and Nrf2, NAD(P)H: quinine oxidoreductase 1 (Nqo1). These results show that 6-SG has a holistic approach and prevention of pigmentary disorders linked with oxidative stress, such as vitiligo[21].

6-shogaol increases the expression of mRNA and proteins of HO-1 and Nrf2, which regulate the antioxidant catalyst, hence inhibiting the formation of intracellular ROS. These findings showed that 6-shogaol may have the ability to prevent both muscle regeneration, which is linked to muscle growth, and muscle atrophy in differentiated muscle damage[22]. Moreover, 6-Shogaol suppressed the UVB radiation-mediated ROS production and increased oxidation inhibitor levels by preventing the exaggeration of Mitogen-Activated Protein Kinase (MAPK) signalling and upregulating the signalling pathway of Nrf2-HO-1 in human epidermal cells (HaCaT)[23]. Another study showed the free radical quenching effect of fresh ginger root and retention of the ginger root at 80^{0}C for two hours against hydroxyl and superoxide radicals. On the preservation of ginger root at 80^{0}C, decreased singlet oxygen and peroxy radical scavenging ability whereas increased superoxide radical scavenging ability than the fresh ginger root. This phenomenon showed, that heat treatment changed the scavenging activity of ginger due to the transformation of 6-Gingerol to 6-Shogaol, so this conversion may increase or diminish the antioxidant potential based on the type of free radical[24].

2.2 Anti-inflammatory Activity

Inflammatory response is the protective mechanism by external stimuli of the human body. Shogaol exerted an anti-inflammatory effect on activated endothelial cells by significantly impairing the ability of leukocytes to bind to lipopolysaccharide and transmigration of THP-1 cells, Moreover, it significantly reduced inflammatory mediators like leukocyte infiltration/ edema formation, proinflammatory mediators such as chemokines, interleukins and altered the expression of MAPKs p38, JNK, ERK, PI3K/Akt, HDAC1, JNK-Nrf2 or PPARγ signalling pathways mediated inflammation of various cell types which was evaluated in both *in vitro* and *in vivo* methods[25,26].

6-Shogaol documented to produce an anti-inflammatory effect by inhibiting the Lipopolysaccharide (LPS)-activated BV2 microglia which are the major immune cells of the brain to produce inflammatory mediators in a concentration-dependent manner, activation of nuclear translocation of NF-κB p65, inhibited phosphorylation and increase PPAR-γ expression[27]. Gout is an inflammatory arthritis that develops when crystals of monosodium urate accumulate within tissues and joints. 6-Shogaol has a significant effect on gout. In addition, Shogaol Solid Lipid Nanoparticles (SSLNs) enhance the solubility and oral bioavailability, potently lowering the level of serum uric acid by inhibiting Xanthine oxidase activity, TNF-α and IL- 1β in gouty arthritis rat model[28]. 6-shogaol possesses a prophylactic effect against liver dysfunction in sepsis by significantly suppressing hepatic inflammatory response through suppressing MAPK/NFκB signalling pathway and also regulates mRNA expression. In addition, it significantly reduces serum Aspartate Transaminase (AST) and Alanine Transaminase (ALT) level[29]. 6- Shogaol induced apoptosis in rheumatoid arthritis Fibroblast Like Synoviocytes (FLS) and MH7A cells and reduced the production of Interleukin- 1β,6,8, TNF-α, MMP-2 & 9. It also inhibits the PI3K/AKT/NFκB pathway by instigating PPAR-γ expression and ameliorates joint destruction of mice with collagen-induced arthritis[30].

In one study, 6-shogaol significantly reduced pro-inflammatory cytokines such as prostaglandins by decreasing the cyclooxygenase enzymes which play an essential role in inflammation in arthritis[31]. Ginger concentrate's anti-inflammatory potential was evaluated in a carrageenan-induced rat paw model, at varying dosages. In a dose-dependent manner, the extract showed a reduction of inflammatory mediator (MPO, MCP-1, TNF-α, PGE2 and IL-6) levels from 32% to 60%. 6-Shogaol exhibits inflammation-attenuating activity at the same concentration as a standard drug,

so it possesses the potent action than other ginger extracts[32].

2.3 Anti-asthmatic Effect

Asthma is a persistent inflammatory airway disorder marked by bronchoconstriction and bronchial hyperresponsiveness. 6-shogaol demonstrated the anti-asthmatic effect in the murine House Dust Time (HDM) animal model of asthma which influences cAMP concentration in CD4 cells, inhibits the NfκB signalling pathway, phosphodiesterases and proinflammatory cytokines in activated CD4 cells[33]. Another study demonstrated the beneficial effect of 6-shogaol attenuates Gq- protein-mediated intracellular calcium and inositol phosphate and inhibits phosholipase β which is an important factor for airway smooth muscle contraction. In addition, a synthetic derivative of M14 has developed the ability to inhibit ach-induced intracellular calcium level in comparison to 6-shogaol, but the compound doesn't relax the airway smooth muscle[34].

2.4 Neuroprotective Activity

The effects of shogaol on the neuroprotective potency of sevoflurane in a rat model of ischemia reperfusion-induced brain injury. After 14 days of oral 6-shogaol administration, the rats in the treatment group underwent ischemia reperfusion-induced brain damage. The 6-shogaol therapy decreased cerebral infarction, brain oedema, and quantity of apoptotic cells, either with or without sevoflurane post-treatment. The PI3K/Akt/mTOR signal pathway was significantly stimulated, according to the western blotting investigation. Studies using western blotting and RT-PCR demonstrated enhanced gene and HO-1 and HIF-1a protein expression. Post-conditioning with sevoflurane, I/R-induced cognitive impairments were lessened, either with or without 6-shogaol therapy. The recent findings showed that 6-shogoal precondition enhanced the cognitive protecting properties of post-conditioning with sevoflurane, proving effective in mitigating I/R-induced tissue damage[35].

When Traumatic Brain Damage (TBI) induces depression-like behaviour and anxiety in rats, 6-shogaol has been shown to have defensive advantages. The expressions of Malondialdehyde (MDA), tumour necrosis factor-α (TNF-α), Brain-Derived Neurotrophic Factor (BDNF) and Interleukin-1β (IL-1β) levels were investigated in brain water and tissues. 6-shogaol therapy managed to reduce depression-like behaviours/anxiety in mice with traumatic brain injury, as well as change MDA formation, lower brain water content and express two important cytokines (TNF-α and IL-1β) that induce inflammation in brain tissue. All of them may help to explain about neurological disorders that follow brain trauma have improved. 6-shogaol may be a promising treatment option for behaviours associated with anxiety and depression brought on by traumatic brain injury[36].

The potential of ginger components in 6-shogaol and 6-paradol was demonstrated using a mouse model of multiple sclerosis which alleviates Experimental

Table 1. Beneficial effects of 6- Shogaol on human health

Biological Activity	Mechanism of Action and Signalling Pathway
Pigmentary disorder	Potentiating the mRNA expression of HO-1, Nrf2 protein expression, and Nqo1 by activation of the Nrf2 signalling pathway.
Neuroprotective effect	Decreased brain oedema, cerebral infarct volume and apoptotic cell counts by Significant activation of PI3K/Akt/mTOR signalling pathway.
Renoprotective effect	Prevents apoptosis and inflammation by activation of NF-κB, reducing IKKαβ/IκBα phosphorylation and induced heme oxygenase- 1 via p8 MAPK activation.
Analgesic effect	Reduced pain by a considerable reduction in spinal cord expression of TRPV1 and NMDAR2B.
Bone resorption activity	Activation of RANKL, JNK signalling axis, osteoclast specific genes of mRNA and NFATc1.
Effect on ulcerative colitis	Significantly reduced Disease Activity Index parameters, regulating the intestinal homeostasis and improving the crypt damages by activation of CD133 and CD4 cells.
Anti-obesity effect	Inhibition of adipokine and adipogenesis-related related gene expression activates AMPK/SIRT1.
Anti-asthmatic effect	Increases cAMP concentration activates proinflammatory cytokines in CD4 cells and inhibits the NfκB signalling pathway.

Autoimmune Encephalomyelitis (EAE). 6-shogaol reduces the disease's outward manifestations as well as remyelination, astrogliosis, decreased cell accumulation in the white matter of the spinal cord, and microglial activation which is essential for immunological responses inside the central nervous system. 6 - Shogaol downregulated the inflammatory mediators, which has a neuroprotective impact[37].

Parkinson's disease is a neuronal degeneration exemplified by movement impairment and dopaminergic neuron loss. Recently most of the PD patients suffer from non-motor symptoms of GI dysfunction (dysphagia, drooling, impaired gastroparesis and bowel dysfunction) associated with disruption of the intestinal epithelial barrier. 6-shogaol demonstrated the neuroprotective property of PD in the C57BL/6J mice model via suppressing the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced damage in the epithelial lining of the gut by the preservation of gut barrier integrity and dopaminergic neurons by enhancing the cell survival signalling pathway[38].

Progression of Alzheimer's dementia correlated with cholinergic neuron loss and deposition of amyloid-β (Aβ). 6-shogaol was reported to activate Sortilin-related receptor-1(SOR-1) which reduced the amyloid precursor protein shedding to secretase the generated Aβ in HT22 cells and APPSw/PS1-dE9 Tg mice[39]. In another study author reported, 6-shogaol has neuroregenerative potential in rat Pheochromocytoma (PC-12) cells by stimulation of PI3K/AKT and MEK/ERK1/2 signalling pathways and mimics the action of neuronal growth factors which possess therapeutic uses in neurodegenerative diseases[40].

2.5 Renoprotective Activity

Using an experimental urolithiasis rat model caused by Ammonium Chloride (AC) and Ethylene Glycol (EG), the anti-urolithic property of 6-Shogaol was explored. Alongside the EG and AC treated group, 6-shogaol markedly lowers blood urea nitrogen levels, Malondialdehyde (MDA), serum creatinine, and uric acid and raises GSH levels. According to histology results, 6-Shogaol prevents kidney damage and significantly reduces the size and quantity of calcium oxalate crystals, restoring normal renal function[41].

A further study demonstrates that 6-Shogaol defends acute kidney injury attributed to cisplatin by alleviating tubular injury and renal dysfunction. This was evaluated by improving histopathological results and lowering blood urea nitrogen and serum creatinine levels. 6-Shogaol also reduces oxidative stress caused by cisplatin, and it regulates the activity of prooxidant and antioxidant enzymes, cytokine production, immune cell infiltration, apoptosis and necroptosis[42]. Compared to other ginger constituents, 6-Shogaol had a conserving influence against acute kidney injury associated with ischemia-reperfusion by lowering plasma creatinine, kidney neutrophil gelatinase-associated lipocalin mRNA production and blood urea nitrogen. Human proximal tubule cells in the kidney 6-Shogol induces heme oxygenase-1 via p8 MAPK activation and dramatically attenuates NF-κB activation by lowering IKKαβ/IκBα phosphorylation, hence preventing inflammation and apoptosis[43].

2.6 Anticancer Activity

Many studies on the anticancer activity of ginger and its phytochemical constituents have revealed that they are active against several kinds of cancer cell types. Recently, the potential target of 6-Shogaol was analysed and found that it inhibited the pathways of Akt, ERK, mTOR, Stat3 and PI3K; it also disrupted the cell cycle by arresting apoptosis in cervical cancer cell lines HeLa and SiHa; and when combined with Baflomycin A1 and Tax, it enhanced the activity of 6-Shogaol and targeted binding with heat-shock 60 kDa protein (HSP60) in A549 cells[44,45]. By directly binding to the AKT signalling pathway, which in turn caused apoptosis and inhibited the Epithelial-Mesenchymal Transition (EMT) process, 6- shogaol inhibited the amplification of the YD-10B, Ca9-22 oral squamous cancer cell line in a dose-responsive way[46].

Using nuclear DNA fragmentation, an increase in the sub G1 population, the potentiation of Polymerase (PARP) cleavage, the intrinsic caspase pathway and upregulating the phosphorylation and expression of GRP-78, CHOP, ATF4, and eIF-2α—all recognised biomarkers of ER stress and also inhibited SW872 cells growth on human liposarcoma cell line[47]. 6-Shogaol exerts the anti-cancer effects by generation of ROS and activation of p53 which induces cell cycle arrest and apoptosis/ downregulates synthesis of fatty acid in lymphoblast cells, also synergistically amplifies the cytotoxic effect of Methotrexate[48]. In

addition, it attenuates the resistance development of 5- Fluorouracil in colorectal cancer cells by activation of AMP-Activated Protein Kinase (AMPK) signalling which recovers the upregulation of sterol regulatory element binding protein- 1 (SREBP-1) is a critical transcriptional factor involved in lipid synthesis and metabolism in adipocyte containing microenvironment medium, and 6-Shogaol enhanced the cytotoxic effect of 5-Flurouracil, Oxaliplatin and Irinotecan by activation of autophagy[49,50].

Another report showed that 6-Shogaol downregulated the Notch signalling pathway in Hes1 and Cyclin D1 genes led to an antiproliferative effect in breast cancer cells through inhibited autophagy and significant accumulation of G2/M phase in cell cycle[51], effectively attenuated NF-κB and AP-1 which inhibits inflammation and cell proliferative markers in 7,12-dimethylbenz[a] anthracene (DMBA) induced hamster oral carcinogenic model[52]. 6- Shogaol exhibited potential antitumor activity in human fibrosarcoma cells of HT1080 by increased ROS production which induced apoptosis, activated AkT/mTOR signaling pathway and decreased glucose uptake[53].

6-Shogaol exerted the antitumor property through attenuation of tumour cell propagation and also induced TNF-Related Apoptosis-Inducing Ligand (TRAIL) mediated cell death which triggered by upregulation of ROS production, tumor suppressor protein expression 53 (p53) and changed the mitochondrial transmembrane potential. It also inhibited the autophagy flux by increased p62 and microtubule-associated proteins 1A/1B light chain 3B-II levels[54]. Toll-Like Receptors (TLRs) play a crucial role in the host immune system, triggering TLR leads to the induction of proinflammatory cytokines and chemokines which activate both innate and adaptive immunity and are also involved in cancer progression. 6-Shogaol Specifically inhibited TLR4 dimerisation induced by LPS leading to activation of NF-κB and COX-2 expression to prevent the progression of cancer and inflammatory responses[55].

6-Shogaol possessed anticancer activity, but in free shogaol was less effective due to poor solubility, oral absorption and rapid metabolism. So the author reported to improve the bioavailability and solubility of 6-shogaol was loaded with micelles of Polyethylene Glycol (PEG) derivative of linoleic acid ($mPEG_{2k}$-LA) to make nanoparticles. Shogaol micelles showed slower release and improved bioavailability when compared with free shogaol which was evaluated in both *in-vitro* and *in-vivo* method[56].

2.7 Antidiabetic Activity

In the Streptozotocin (STZ)-induced mouse model, 6-shogaol demonstrates an anti-diabetic effect by significantly lowering blood glucose, AST, and ALT levels, which indicate liver damage, and reducing the expression of TNF-α and TNF-β1 mRNA, ki-67, a protein linked to cell proliferation, and the proapoptotic protein caspase3. 6-Shogaol reverses the

Table 2. Mechanism of action and anticancer activity of 6-Shogaol

Cancer cells	Activity	Signalling pathway
Cervical cancer cell line (HeLa, SiHa) and Oral squamous carcinoma cell (YD-10B, Ca9-22)	Suppression of the EMT process, apoptosis induction, cell cycle arrest, and reduced cell proliferation.	Prevents the signalling pathways for Akt, PI3K, Stat3, ERK, and mTOR.
Liposarcoma cell (SW872)	Enhanced the sub G1 population and caused apoptosis by nuclear DNA breakage.	PARP cleavage and intrinsic caspase pathway activation.
Breast cancer cell	Inhibited autophagy and significant accumulation of the G2/M phase in the cell cycle	Downregulated notch signalling pathway
Fibrosarcoma cells (HT1080)	Increased ROS production which induced apoptosis and decreased glucose uptake	Activated Akt/mTOR signalling pathway
Colorectal cancer cell	Attenuates resistance development and enhanced activity of 5- Fluorouracil, Oxaliplatin and Irinotecan by upregulation of (SREBP-1) is a factor involved in adipocyte lipid synthesis and metabolism.	Activation of AMPK signalling

formation of sinusoids with inflammatory cell display, fatty alteration, and core region necrosis caused by STZ[57]. Vascular calcification is a major cardiovascular complication which mimics the hyperglycemic environment through activation of NLRP3/IL-β inflammasome and Akt signalling pathway. 6-shogaol significantly attenuates these signalling pathways and human artery smooth muscle cell calcification which reduces the concentration of glucose[58].

2.8 Analgesic Activity

Ginger's abundant bioactive constituents, gingerol and shogaol, have been used to relieve pain, including dysmenorrheal discomfort[59]. 6-Shogaol was evaluated the analgesic effect by dietary supplementation (SNL+ 0.75% Shogaol) in a rat model with Spinal Nerve Ligation (SNL) for 30 days significantly reduced pain, anxious behaviour, circulating cell-free mitochondrial DNA (ccf-mtDNA) and increased gut-derived metabolite levels, which assessed gut-brain pain management[60]. In addition, Balb/C mice orally administered ginger extract (400mg/kg/day) and 6-Shogaol (15mg/kg/day) for 49 days were significantly suppressing the spinal cord expression of TRPV1 and NMDAR2B which reduced pain in diabetic neuropathy[61].

2.9 Bone Resorption Activity

Bone resorption activity of 6-Shogaol was investigated by using Bone Marrow Macrophages (BMM) and Sprague-Dawley rat (intraperitoneal injection – 100mg/kg and intragingival injection – 25mg/kg) for 28 days. 6-Shogaol triggered the activation of RANKL, C- Jun N Terminal Kinases (JNK) signalling axis, and NFATc1, which in turn promotes osteoclast differentiation, demineralisation of alveolar bone, and formation of F-actin rings in BMM. Using this method *in vivo* also expedites the movement of orthodontic teeth and promotes alveolar bone transient osteopenia[62]. The probable carcinogen for renal cell carcinoma with bone metastases is 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP). On 786-O cells, 6-Shogaol pretreatment inhibited PhIP-mediated bone resorption and promoted osteoclastogenesis[63].

Another study demonstrated the anti-resorptive properties of Shogaol by *in-vitro* and *in-vivo* approach. 6-Shogaol inhibited RANKL-induced MAPK activation, Ca^{2+} signalling, and ROS generation by inhibiting the signalling pathways, which greatly decreased osteoclast development, actin ring formation, and resorption in mouse bone marrow cells grown in culture. By reducing the amount of macrophages and neutrophils generated by ligation, together with the levels of Inteleukin-1β and TNF-α in the periodontitis mouse model, it inhibits osteoclastogenesis and alveolar bone resorption[64].

2.10 Shogaol Effect on Ulcerative Colitis

Shogaol has the clinical benefit on Disodium Sulfate (DSS) induced ulcerative colitis mouse model by significantly reduced Disease Activity Index parameters (i.e., blood in stool, rectal bleeding and diarrhoea) score and histopathological examinations showed 6-Shogaol reversed the colonic injury triggered by DSS. It showed a better effect than 6-Thioguanine which is used as an immunosuppressive chemotherapeutic agent through intestinal regeneration, regulating intestinal homeostasis and improving the crypt damages by activation of CD133 and CD4 cells[65-67]. In addition, 6-Shogaol and its metabolites M2, and M13 nanoparticles exhibited potent action on the target site of ulcerative colitis by downregulating the release of pro-inflammatory mediators and enhancing anti-inflammatory factors[68,69].

2.11 Shogaol Effects on Obesity

Anti-obesity activity of Shogaol was investigated by using C57BL/6J mice nourished through a lipid-rich diet. It reduced obesity degree, blood lipid level and improved glucose homeostasis. In addition, it decreased the ratio of bacteroides and firmicutes and enhanced the diversity of gut microbiota[70]. 6-Shogaol showed potential antiobesity activity in obesogenic diet mouse model by a significant reduction of body weight, inguinal fat mass and epididymal fat, inhibition of adipogenesis-related genes (PPAR- γ, FAS, C/EBP-1α, SREBP-1c,) and adipokine expression which is responsible for lipid accumulation and also activates AMPK/SIRT1 which is target for obesity treatment[71,72].

Another study demonstrated the therapeutic efficacy of 6-Gingerol and 6-Shogaol via molecular docking studies has the best binding affinity with β3-Adrenergic receptor (-82.364kcl/mol and -79.987kcal/mol). This study revealed that 6-Shogaol possessed less anti-obesity effect than 6-Gingerol[73].

2.12 Antimicrobial Activity

Ginger possesses antimicrobial activity against various microbes. 6-Shogaol exhibited potent antifungal and antibiofilm formation effects against *Candida* strains (*Candida albicans* and *Candida auris*) and fluconazole-resistant *Candida* strains which are causative agents for Candidiasis. Biofilm formation enhances the protective effect of pathogens and develops resistance against drugs. 6-Shogaol (10µg/ml) significantly inhibited the planktonic cell growth, hyphal cell growth and biofilm formation by inducing the expression of several transporters (CDR1, CDR2 and RTA3) and genes (ECE1, HWP1) and also reduce the virulence of strain without causing toxicity to the cells[74,75]. So, these studies showed that 6-Shogaol has potent antifungal, anti-biofilm and anti-virulence activity against *C.* strains. On the other hand, 6-Shogaol increases the Interferon-γ (IFN-γ) expression which is a critical cytokine exhibiting immunoregulatory (cellular and humoral immune response) effects against bacterial and viral infections[76]. Another study investigated the antimicrobial activity of various phytochemical compounds via molecular docking and *in-vitro* studies with known antibiotics against *Staphylococcus aurus.* From this study, Shogaol has a strong interaction with SaHPPK protein and possesses a docking score of 55.48 than the other known antibiotics (amoxicillin- 41.98). In the *in-vitro* studies, Shogaol exhibited a greater inhibitory effect at a concentration of 50µg/ml. It is hence concluded that Shogaol has a beneficial and therapeutic effect against SaHPPK[77].

2.13 Antiemetic Activity

Ginger is commonly used to relieve gastrointestinal distress, particularly emesis brought on by chemotherapy[78,79]. Using *ex vivo* gastroesophageal-vagal preparations obtained from Pirt-GCaMP6 transgenic mice, used to assess the inhibitory potential of 6-Shogaol against vincristine-induced effect on gastroesophageal afferent nerve endings by reducing the activation response of TRPA1 and 5-HT3 receptors, which was compared with 5-HT3 receptor antagonist Palonosetron[80].

3. Safety and Toxicity Studies of Shogaol

The compound Shogaol from ginger is used as a herb for medicine and in various cuisines. The safety of ingesting ginger or ginger extracts at varying dosages has been assessed in numerous clinical investigations, but not as an isolated compound. Although 6-shogaol has demonstrated low toxicity in animal models and normal human cells, comprehensive clinical research on its safety in people is lacking. According to the studies Shogaol has low toxicity in both animal models[41] and normal cells[45-48] (such as human colon, lung, liver, and dermal fibroblast cells). It even exhibits selective toxicity against cancer cells, which makes it a possible treatment option for cancer. As far as we are aware, there have been no published clinical trials examining the toxicity or safety of 6-shogaol in humans. Some research has been done on its pharmacokinetics and metabolism in humans. 6-shogaol is widely degraded in the body, as those investigations showed, and its metabolites may have distinct toxicity profiles and biological functions. Some studies show how human Cytochrome P450 (CYP) 1A2, 2C9, 2C19, 2D6, and 3A4 interact molecularly with 6-shogaol and other ginger components[81,82]. The toxicity, distribution, metabolism, excretion and absorption of those ginger components were estimated using computational methods and literature searches. Their research suggests that components of ginger may influence the expression and function of different human CYPs, changing the way drugs are eliminated and their effects.

4. Conclusion

Ginger is an old root that has long been revered, due to its many useful culinary, medicinal, cultural and aromatic qualities. It can be utilised in different forms including dried, powdered, fresh and crystallised. Ginger is rich in fibre, vitamins, minerals and phytoconstituents. Ginger has a pungent principle because of the presence of major medicinally active phytoconstituent Gingerol and Shogaol. Since being discovered in the early twentieth century, the primary bioactive compound found in dried rhizomes of

Zingiber officinale Roscoe, 6-Shogaol, has been comprehensively analysed. Numerous researches have documented its pharmacological benefits, including antioxidant, antibacterial, antiviral, reducing pain and inflammation, suppressing or preventing the growth of cancer cells, boosting the immune system, facilitating digestion and lessening nausea and vomiting. Therefore, Shogaol has the potential effects to improve human health.

5. Future Perspectives

Shogaol's varied biological activities make it a promising substance in many sectors. Its complete potential and the development of useful applications will depend on ongoing research and development.

6. Authors Contribution

Hemnath Elango - Conceptualisation and Supervision; Archana Vellingiri – Writing: Original draft preparation; Arsha Surendran, Shalini Karunanithi – Review and Editing. All authors have read and agreed to the published version of the manuscript.

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